

## **DIVISION DIRECTOR MEMORANDUM**

**Date:** August 7, 2003

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**To:** Members, Pulmonary-Allergy Drugs Advisory Committee

**Subject:** Overview of the FDA background materials for NDA 21-573, Ariflo (cilomilast) Tablets, 15 mg, for the maintenance of lung function (FEV1) in patients with chronic obstructive pulmonary disease (COPD)

Thank you for your participation in the Pulmonary-Allergy Drugs Advisory Committee (PADAC) meeting to be held on September 5, 2003. As members of the PADAC you provide important expert scientific advice and recommendation to the US Food and Drug Administration (the Agency) on the regulatory decision making process related to the approval of a drug product for marketing in the United States. The upcoming meeting is to discuss the NDA from GlaxoSmithKline (GSK), seeking an approval for cilomilast 15 mg to be administered twice daily for the maintenance of lung function (FEV1) in patients with chronic obstructive pulmonary disease (COPD) who are poorly responsive to albuterol (increase in FEV1 of  $\leq 15\%$  or  $\leq 200$  mL).

Cilomilast (also referred to as SB 207499) is a phosphodiesterase-4 (PDE-4) inhibitor. This is a new molecular entity and a new drug class for the treatment of COPD. Cilomilast is pharmacologically related to theophylline, which is a non-specific phosphodiesterase (PDE) inhibitor. No PDE-4 inhibitor is approved for use in humans in the United States. The proposed commercial name of cilomilast is Ariflo. The drug product is an immediate release tablet. The proposed dose is 15 mg twice daily.

Attached are the background materials for the meeting. The background materials include several documents prepared by the Agency, the applicant's proposed product label for cilomilast, a product label of theophylline, and a review article on COPD. The documents prepared by the Agency include a summary of the major clinical studies conducted by GSK to demonstrate efficacy and safety of cilomilast in COPD patients, a summary of some relevant pharmacokinetic studies, and a summary of relevant preclinical data. The documents prepared by the Agency contain findings and opinions based on reviews of the Applicant's submissions. These represent preliminary findings, and do not represent the final position of the Agency. Indeed, an important piece of our thinking on this application will be the opinions and the input that we receive from you at this meeting.

Subsequent sections of this memorandum summarize some relevant preclinical data, the COPD clinical program of cilomilast, and the key issues and questions for discussion at the PADAC meeting.

**Preclinical data**

As in any NDA program, cilomilast was studied in various animal species to assess the toxicity profile. In these studies, a safety margin was calculated. A safety margin of 1.0 indicates that the mean level of human AUC exposure is equal to the mean level of animal AUC exposure at which there were no adverse effects. Ideally, drugs that are approved for use in humans have preclinical safety margins of several fold, particularly if the benefits of those drugs are modest or if the condition being treated is non-lifethreatening. The Agency also considers the toxicity finding noted in the animal and determines whether clinical monitoring can be used to reliably detect a given dose-limiting toxicity in humans, and if this is the case, an acceptable safety margin may approach a level of 1.0 or even go slightly below 1.0.

Toxicologic studies of cilomilast in laboratory animals reveal several findings of concern where safety margins were below 1.0. The safety margin for testicular toxicity (manifested as degeneration of the seminiferous epithelium) was 0.2 in the most sensitive species (the rat). This toxicologic finding was also noted in other species at higher exposures. Cilomilast also induced changes in the adrenal cortex in rats at a safety margin less than 1.0, and focal myocardial necrosis in rats at a safety margin of 0.5. Adrenal cortex changes and myocardial necrosis were also observed in other species at higher exposures. Gastrointestinal disturbances, with emesis and erosion of the gastrointestinal mucosa, were observed in all three tested species (rat, mouse, and monkey) at a safety margin ranging from 0.2 to 0.5.

These findings, while very concerning, have been partially addressed by additional clinical data submitted by the sponsor. Moreover, time considerations for the panel meeting preclude an in depth discussion of each potential preclinical toxicity concern. The major preclinical concern that we would like the panel to address is that of vasculitis. Vasculitis was observed in multiple organs in rats and mice at a safety margin of 7.0 (for the mouse) and with no safety margin (0.2) for rats. This finding was irreversible. Vasculitis is a preclinical finding that is known to occur with the PDE-4 inhibitors as a class, and it is of significant clinical concern given its association with serious morbidity and mortality and the fact that it is impossible to effectively monitor patients and prevent an episode. Ariflo causes vasculitis in animals and the preclinical data provide no assurance that this event will not occur in humans. The clinical database must therefore be relied upon heavily to remove this concern.

**Clinical program**

The cilomilast clinical development program was reasonably large. To date 66 clinical studies with cilomilast have been conducted by GSK, including studies conducted on asthma and COPD patients. The core COPD clinical program consist of 12 studies, of which 2 were dose-ranging studies, 4 were well-controlled efficacy and safety studies (the pivotal studies), 3 were mechanism of action studies, 1 was a cardiac safety study, and 2 were open-label long term extension safety studies. Approximately 6,500 patients have participated in the cilomilast clinical program. Approximately 4,400 patients have been exposed to cilomilast including approximately 2,200 patients in controlled COPD studies. The mean age of the

patients in the COPD program was 59 years, the patients had approximately 49 pack-years of cigarette smoking, and approximately 96% patients were Caucasians.

#### Dose-ranging studies

GSK conducted 2 dose-ranging studies (studies 38 and 32) in COPD patients. Both studies were very similar in design. Both were double-blind, placebo-controlled, parallel-group studies. Study 38 was conducted in North America, was 4 weeks in duration, and tested 2.5 mg and 5 mg twice daily doses of cilomilast. Study 32 was conducted in Europe, was 6 weeks in duration, and tested 5 mg, 10 mg, and 15 mg doses of cilomilast taken twice daily. The diagnosis of COPD was based on American Thoracic Society (ATS) guidelines. Patients were required to have at least a 10 pack-year cigarette smoking history, a pre-bronchodilator FEV1/FVC ratio of less than 0.7, post-bronchodilator FEV1 30-70% predicted, and post-bronchodilator reversibility of less than 15% or 200 mL. Patients enrolled in the studies had a pre-bronchodilator FEV1 ranging from 1.30 to 1.46 L, and albuterol reversibility ranged from 8% to 11%. In study 38, a total of 75 patients received placebo, and 149 patients received cilomilast. In study 32, a total of 106 patients received placebo, and 318 patients received cilomilast. The primary endpoint in these studies was change from baseline to week 4 or week 6 in trough FEV1.

In study 38, all groups showed a small decrease or no change in FEV1. At endpoint, the mean decrease was 30 mL for placebo group, 0 mL for 2.5 mg group, and 20 mL for 5 mg group. The differences were not statistically significant. In study 32, the active treatment groups showed a relative increase in FEV1. At endpoint, the mean FEV1 decreased 20 mL for placebo group, increased 40 mL for 5 mg group, stayed unchanged for 10 mg group, and increased 120 mL for 15 mg group. Based on these dose-ranging studies, GSK proceeded with the 15 mg twice daily dose in the pivotal studies.

Plasma concentration of cilomilast was measured in the dose ranging studies. Plasma concentration increased dose proportionately.

#### Pivotal efficacy and safety studies

GSK conducted 4 pivotal efficacy and safety studies (Studies 39, 42, 91, and 156). All 4 studies were very similar in design. All were multinational, multicenter, double-blind, placebo-controlled, parallel-group studies that compared 15 mg cilomilast to placebo. All studies were 24 weeks in duration. Study 39 was conducted in US, Canada, and Mexico; study 42 was conducted in UK, Germany, Spain, Australia, New Zealand, and South Africa; study 91 was conducted in various Western European countries; and study 156 was conducted in US and Canada. The criteria used for the diagnosis of COPD were same as the criteria used in the dose-ranging studies. The demographics of the patients enrolled in the studies and the disease severity, including pre-bronchodilator FEV1 and albuterol reversibility were similar across the 4 studies, and were comparable to the 2 dose-ranging studies. The 4 studies were large. The number of patients randomized was 647 in study 39, 700 in study 42, 711 in study 91, and 825 in study 156. The randomization was 2:1 (drug:placebo) in studies 39, 42, and 91, and 1:1 in study 156.

The primary efficacy endpoints in all studies were change from baseline in the trough FEV1 and change from baseline in total score of the St George's Respiratory Questionnaire (SGRQ). These were declared as co-primaries. The studies also had a host of secondary and tertiary endpoints that included trough FVC, post-exercise breathlessness (modified Borg scale), symptom score, 6-minute walk, COPD exacerbation, rescue medication use, and symptom free days. Safety was assessed by recording of adverse events, physical examination, clinical laboratory measure, ECG recording, and Holter monitoring in a subset of the study patients. Some of the secondary and tertiary variables were defined slightly differently in study 156 as compared to the other three studies.

One feature in the studies that is noteworthy is that the patients were withdrawn from the study if the study medication compliance was not in the range of 80-120%, inclusive. Generally a greater percentage of placebo patients than cilomilast treated patients were compliant, primarily because a larger percentage of cilomilast treated patients withdrew prematurely from the study due to gastrointestinal adverse events. Therefore, the efficacy data reflects those patients who were able to tolerate the drug and stay in the study.

The mean FEV1 for cilomilast treated patients increased in three of the four studies. Compared to baseline FEV1, the endpoint FEV1 increased by 10 mL in study 39, 30 mL in study 42, stayed unchanged in study 91, and increased by 10 mL in study 156. The differences in FEV1 change between the cilomilast and placebo group was 40 mL in study 39, 30 mL in study 42, 30 mL in study 91, and 30 mL in study 156. The difference between the cilomilast group and placebo group reached statistical significance in study 39 and study 156, but did not reach significance in the remaining two studies. The difference between cilomilast and placebo groups was larger than the actual FEV1 increase in the cilomilast group because the FEV1 declined somewhat in the placebo group. The decline in FEV1 in the placebo group was noted mainly in the first 2-4 weeks of the studies and is difficult to explain.

The mean SGRQ score decreased (decrease is better) in all studies for cilomilast treated patients. Compared to baseline, the mean change from baseline in the SGRQ decreased by -3.7 in study 39, -4.2 in study 42, -2.7 in study 91, and -3.2 in study 156. The difference in SGRQ change between the cilomilast and placebo group was -4.1 in study 39, +0.7 in study 42, -0.4 in study 91, and -1.9 in study 156. The difference between the cilomilast and placebo group reached statistical significance in study 39 and study 156. The SGRQ score crossed the threshold (-4 is accepted as the minimum important difference) of clinical significance only in study 39.

The differences between the cilomilast and placebo group for the secondary and tertiary variables were not remarkable, but for some they tended to favor cilomilast. Trough FVC generally trended along with FEV1. Rescue albuterol use was slightly less in the cilomilast group compared to the placebo group. The difference ranged from 0.02 to 0.21 puffs/day. The percent of symptom free days was slightly greater in the cilomilast group compared to the placebo group. The difference ranged from 0.6 to 0.9 percent symptom free days.

The most prominent adverse events noted in the controlled studies were nausea, diarrhea, abdominal pain, dyspepsia, and vomiting. These adverse events were 2 to 3 fold more frequent in the cilomilast treated patients compared to the placebo treated patients. The frequency of these adverse events ranged from 1% (vomiting) to 6% (diarrhea) in placebo treated patients compared to 5% (dyspepsia, vomiting) to 13% (diarrhea, nausea) in cilomilast 15 mg twice daily treated patients. Withdrawals due to adverse events were dominated by similar adverse events. The common reasons for withdrawals were nausea (placebo 0.4% vs cilomilast 15.7%), abdominal pain (placebo 0.5% vs cilomilast 3.3%), diarrhea (placebo 0.4% vs cilomilast 3.6%), vomiting (placebo 0.2% vs cilomilast 3.3%), and dyspepsia (placebo 0.1% vs cilomilast 1%).

### **Key issues and questions**

The magnitude of the effects seen on the efficacy variables, particularly on FEV1, is a key point for discussion at the PADAC meeting. In the two studies, study 39 and 156, where the difference between cilomilast and placebo was statistically significant, the differences between the groups in mean change from baseline for each group were 40 mL and 30 mL, respectively. Although the difference reached statistical significance in these two studies, the separation between the two groups was primarily driven by an early decrease of FEV1 in the placebo group, which is difficult to explain. In these two studies, the increase in FEV1 as a mean change from baseline within the cilomilast treated group was 10 mL. The difference between the groups in the SGRQ score also reached statistical significance in these two studies, but only in study 39 did the difference cross the 4-unit threshold that is considered to be clinically meaningful. To place these numbers in perspective, the Agency had requested that GSK include a theophylline control arm in their final study (study 156), but this suggestion was not pursued.

Theophylline is a non specific PDE inhibitor, whereas cilomilast is specific for PDE-4, which supposedly would increase target specificity to the airway. Theophylline has been used for a long time in the treatment of COPD. Some perspective on the efficacy of theophylline, a drug that you are familiar with, is helpful in assessing the clinical relevance of the efficacy of cilomilast although clearly the theophylline studies were in different patients, at a different time, with different study designs. A 2002 meta-analysis addressing the efficacy of theophylline for the treatment of COPD was published in the Cochrane Database of Systemic Reviews.<sup>1</sup> A total of 20 randomized studies met the selection criteria for including patients with COPD, and included a randomized, double-blind comparison of theophylline to placebo. Baseline FEV1 in these studies ranged from 0.96 L to 1.15 L. All 20 studies were crossover design in nature. Five studies used a short acting theophylline preparation and the remaining 15 studies used long acting sustained release theophylline preparations. Thirteen studies with a total of 244 patients contributed data to an FEV1 outcome that showed a statistically significant mean improvement of 100 mL (95% confidence interval from 40 L to 160 mL). Eleven studies with 196 patients contributed data to FVC outcome that showed a statistically significant improvement of 210 mL (95% confidence interval from 104 L to 320 mL). In conclusion, this meta-analysis of 20 studies shows that the FEV1 effect for theophylline in patients with COPD appears to be on the order of about 100 mL. The initial three pivotal trials with cilomilast were designed to demonstrate an FEV1 difference between cilomilast and placebo of 120 mL (likely due to the promising efficacy of cilomilast shown in the dose

ranging study 32), with the final trial (study 156) designed to demonstrate of 50 mL difference. The results of these trials ultimately demonstrated an actual effect on FEV1 of about 30-40 mL.

Another key point of discussion at the PADAC meeting will be the overall safety of cilomilast, specifically gastrointestinal safety. Mesenteric arteritis was seen in rats during pre-clinical studies with cilomilast. Some other drugs of this class are also known to be associated with vasculitis in animals. Mesenteric arteritis in humans is worrisome and this is an unmonitorable adverse event. Furthermore, the gastrointestinal complaints that are so common with cilomilast may mimic the symptoms of early mesenteric arteritis. To get a better handle on the potential risk of cilomilast to cause mesenteric arteritis in humans a system was implemented in the clinical studies that would lead to early and aggressive colonoscopic examination in some patients. Patients with gastrointestinal symptoms (e.g., bloody or black stool, abdominal discomfort, diarrhea, or vomiting) that caused them to be concerned or interfered with daily activities (including eating and sleeping) were to screen themselves with fecal occult blood testing and were also to be assessed by the clinical investigator within 24 hours. A positive fecal occult blood test in such symptomatic patients was to signal the need for a colonoscopy.

The frequency of gastrointestinal symptoms that concerned the patients or interfered with daily activities was three times greater in cilomilast treated patients (12% or 264 patients) compared to placebo treated patients (4.2% or 56 patients). Unfortunately fecal occult blood testing was not promptly done (within 24 hours) in these patients and for some it was not done at all. In the cilomilast group, out of the 264 patients with gastrointestinal symptoms of concern, 154 (58%) patients had fecal occult blood data, of which 15 (9.7%) were positive. In the placebo group, out of the 56 patients with gastrointestinal symptoms of concern, 31 (55%) patients had fecal occult blood data, of which 6 (19.4%) were positive. Some of these patients (10 out of the 21 symptomatic patients eligible for colonoscopy due to positive fecal occult blood results), and also other patients, such as some of those subjects who developed frank melena, had colonoscopies done. A total of 19 colonoscopies were performed in all randomized subjects, with unremarkable findings, and no patient was diagnosed with vasculitis. The failure of rigorous and timely fecal occult blood testing and rigorous and timely follow up with colonoscopy, however, does not give a large safety data base upon which to draw a firm conclusion.

The purpose of the PADAC meeting is to discuss the efficacy and safety data that have been provided to support the approval of cilomilast for the treatment of COPD in the United States. The main issues for the PADAC to consider are the overall risk-benefit assessment of cilomilast for the treatment of COPD. We are asking for detailed deliberation on the clinical relevance of the magnitude of the effect seen on the efficacy variables, and on the adequacy of overall safety data base to assure patient safety.

At the PADAC meeting, the Applicant will present an overview of the efficacy and safety data on cilomilast, followed by the Agency's presentation. The Agency will then present a

brief review of preclinical concerns regarding vasculitis, followed by a clinical overview of efficacy and safety.

Please keep in mind the following questions that will be discussed and deliberated upon following the presentations and discussion.

1. Has cilomilast at a dose of 15 mg twice daily shown a magnitude and consistency of efficacy this is sufficient to support approval of cilomilast for the maintenance of lung function (FEV1) in patients with COPD?
  - a) If not, what further efficacy data should be obtained?
2. Is the safety database (aside from the concern for vasculitis) for cilomilast for the maintenance of lung function (FEV1) in patients with COPD sufficient to support approval?
  - a) If not, what further safety data should be obtained?
3. Do you feel that the concern of mesenteric vasculitis has been adequately studied to be dismissed as a safety concern in humans?
  - a) If not, what further data should be obtained?
4. Do the efficacy and the safety data provide substantial and convincing evidence that support the approval of cilomilast at a dose of 15 mg twice daily for the maintenance of lung function (FEV1) in patients with COPD?

Please note that the questions above are preliminary and may change prior to the meeting. Final questions will be available at the meeting. We intend that all questions above should generate a binary yes or no answer, and will be voted on by the voting members of the Committee.

We look forward to a very interesting meeting and again thank you for your time and commitment in this important public health service.

<sup>1</sup>Cochrane Database Syst Rev 2002;(4):CD003902. Review.